REMARKS

This Amendment corrects an obvious typographical error in claims 1 and 13. Support for this correction is found in the illustrative compounds of the Examples, such as Example 37, and in the description of G itself ("iminodiacetic acid ester groups"). Claims 1-13 are pending. A version with markings showing changes made is attached as an Appendix.

Examiner Lewis is thanked for the courtesies extended to the undersigned during a telephonic discussion held January 31, 2003. During the teleconference the Examiner explained that claim 1 appeared not to read on compound 37 due to the description of G in claim 1.

This Amendment rewrites claims 1 and 13 in direct response to the Patent Office Communication and the January 31, 2003 teleconference with the Examiner. More specifically, G has been corrected in those claims. Claims 1, 4, 5, 8, 10 and 11 now read on the elected species of compound 37.

It is not believed any fee is required for entry and consideration of this Amendment. Nevertheless, the Commissioner is

authorized to charge our Deposit Account No. 50-1258 in the amount of any such required fee.

Respectfully submitted,

James C. Lydon
Reg. No. 30,082

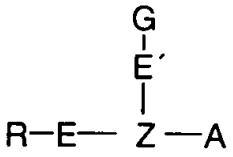
Atty. Case No.: TUR-106
100 Daingerfield Road, Suite 100
Alexandria, Virginia 22314
Telephone: (703) 838-0445
Facsimile: (703) 838-0447

Attachment:
Appendix

APPENDIX

Version with Markings Showing Changes Made

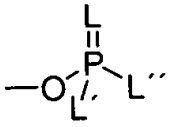
1. (Once Amended) A labeling reactant of formula (I) suitable for labeling an oligonucleotide



(I)

characterized in that

R is a temporary protecting group such as 4,4´dimethoxytrityl (DMTr), 4-methoxytrityl (MMTr), trityl (Tr), (9-phenyl)xanthen-9-yl (pixyl) or not present;

A is either a phosphorylating moiety  where

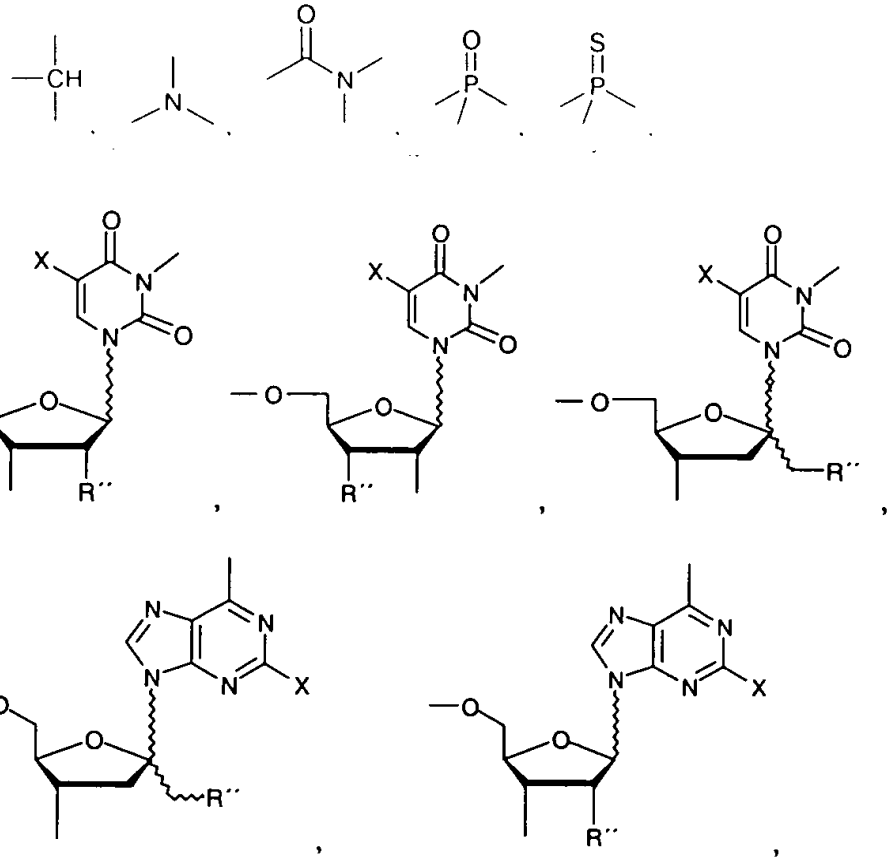
L is O, S, or not present

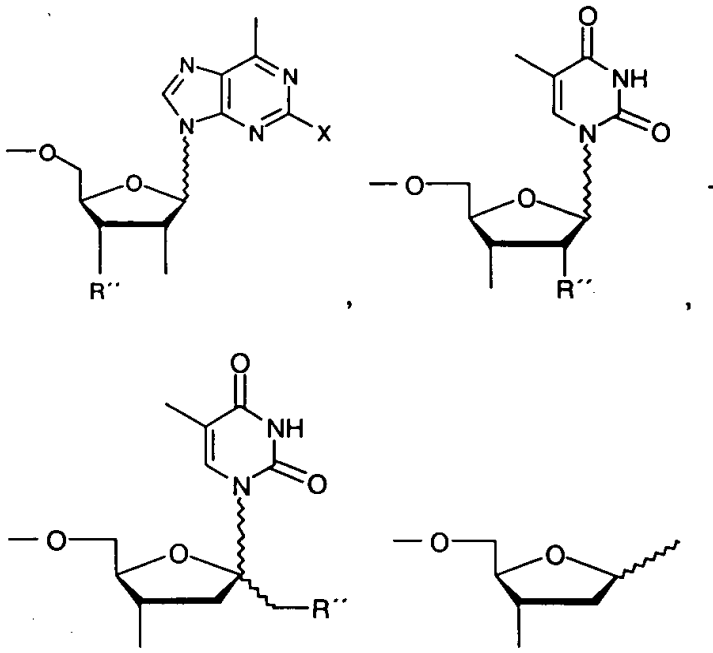
L´ is H, L´´´CH_2CH_2CN or L´´´Ar, where Ar is phenyl or its substituted derivative, where the substituent is nitro or chlorine, and L´´´ is O or S;

L´´ is O^-, S^-, Cl, $N(i\text{-}Pr)_2$; or

A is a solid support tethered to **Z** via a linker arm, which is formed of one to ten moieties, each moiety being selected from a group consisting of phenylene, alkylene containing 1-12 carbon atoms, ethynediyl (-C≡C-), ether (-O-), thioether (-S-), amide (-CO-NH-, -NH-CO-, -CO-NR´- and -NR´-CO-), carbonyl (-CO-), ester (-COO- and -OOC-), disulfide (-S-S-), diaza (-N=N-), and tertiary amine (-N-R´), wherein R´ represents an alkyl containing less than 5 carbon atoms;

Z is a bridge point and is formed from





or trivalent derivatives, substituted or unsubstituted, of cyclohexane, cyclohexene, cyclohexadiene, phenyl, cyclopentane, cyclopentene, cyclopentadiene, cyclobutane, cyclobutene, cyclobutadiene, aziridine, diaziridine, oxetane, thietaneazete, azetidine, 1,2-dihydro-1,2-diazete, 1,2-diazetidine, furan, tetrahydrofuran, thiophene, 2,5-dihydrothiophene, thiolane, selenophene, pyrrole, pyrrolidine, phosphole, 1,3-dioxolane, 1,2-dithiole, 1,2-thiolane, 1,3-dithiole, 1,3-dithiolane, oxazole, 4,5-dihydrooxazole, isoxazole, 4,5-dihydoisozaole, 2,3-dihydroisoxazole, thiazole, isothiazole, imidazole, imidazolidine, pyrazole, 4,5-dihydropyrazole, pyrazolidine, triazole, pyran, pyran-2-one, 3,4-dihydro-2H-pyran, tetrahydropyran, 4H-pyran,

pyran-4-one, pyridine, pyridone, piperidine, phosphabenzene, 1,4-dioxin, 1,4-dithiin, 1,4-oxathiin, oxazine, 1,3-oxazinone, morpholine, 1,3-dioxane, 1,3-dithiane, pyridazine, pyrimidine, pyrazine, piperazine, 1,2,4-triazine, 1,3,5-triazine, 1,3,5-triaza-cyclohexane-2,4,6-trione; where

R′′ is H or X′X′′, where

X′ is -O-, -S-, -N-, ON- or -NH- and X′′ is a permanent protection group such as *t*-butyldimethylsilyl-, tetrahydropyranyl, 1-(2-fluorophenyl)-4-methoxypiperidin-4-yl-, 1-[2-chloro-4-methyl)phenyl]-4-metoxypiperidin-4-yl-, 4-methoxytetrahydropyran-4-yl-, pthaloyl-, acetyl, pivaloyl-, benzoyl-, 4-methylbenzoyl, benzyl-, trityl or

X′ is -O- and X′′ is alkyl or alkoxyalkylalkyl;

X is H, alkyl, alkynyl, allyl, Cl, Br, I, F, S, O, $NHCOCH(CH_3)_2$, $NHCOCH_3$, NHCOPh, SPh_3, $OCOCH_3$ or OCOPh;

E is a linker arm between **R** and **Z**, and is formed of one to ten moieties, each moiety being selected from a group consisting of phenylene, alkylene containing 1-12 carbon atoms, ethynediyl (-C≡C-), ether (-O-), thioether (-S-), amide (-CO-NH-, -NH-CO-, -CO-NR′- and -NR′-CO-), carbonyl (-CO-), ester (-COO- and -OOC-), disulfide (-S-S-), diaza (-N=N-), and tertiary amine (-N-R′),

wherein R′ represents an alkyl containing less than 5 carbon atoms, or not present;

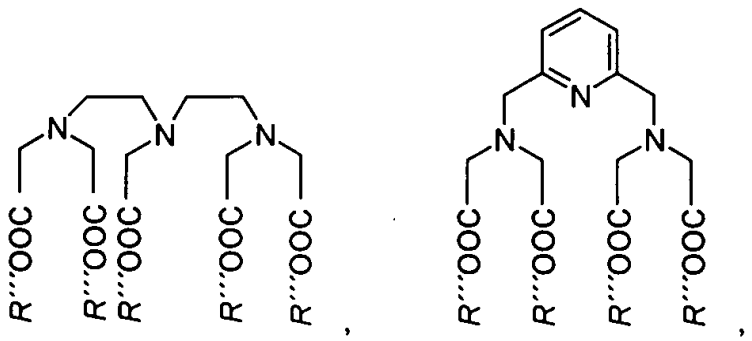
E′ is a linker arm between **G** and **Z**, and is formed of one to ten moieties, each moiety being selected from a group consisting of phenylene, alkylene containing 1-12 carbon atoms, ethynediyl (-C≡C-), ether (-O-), thioether (-S-), amide (-CO-NH-, -NH-CO-, -CO-NR′- and -NR′-CO-), carbonyl (-CO-), ester (-COO- and -OOC-), disulfide (-S-S-), diaza (-N=N-), and tertiary amine (-N-R′), wherein R′ represents an alkyl containing less than 5 carbon atoms, or not present;

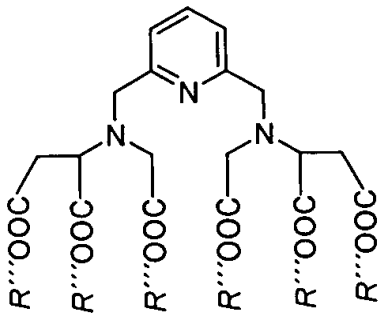
G is a bivalent aromatic structure, tethered to two iminodiacetic acid ester groups [$N(COOR'''_2$] $\underline{N(CH_2COOR''')_2}$ where

R′′′ is an alkyl of 1 to 4 carbon atoms, allyl, ethyltrimethylsilyl, phenyl or benzyl, which phenyl or benzyl can be substituted or unsubstituted, and

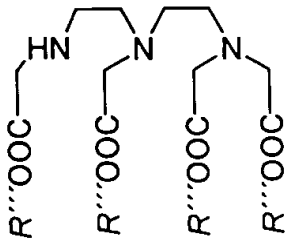
said bivalent aromatic structure is capable of absorbing light or energy and transferring the excitation energy to a lanthanide ion after the solid phase synthesis made labeling reactant has been released from the used solid support, deprotected and converted to a lanthanide chelate, or

G is a structure selected from a group consisting of





and



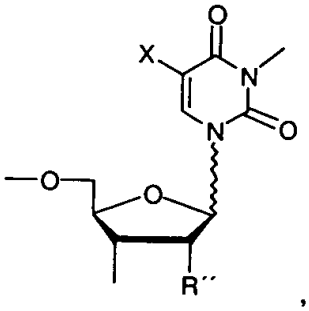
,

where

R$'''$ is an alkyl of 1 to 4 carbon atoms, allyl, ethyltrimethylsilyl, phenyl or benzyl, which phenyl or benzyl can be substituted or unsubstituted, and

one of the hydrogen atoms is substituted with E′, or

G is a protected functional group, where the functional group is amino, aminooxy, carboxyl, thiol, and the protecting group is pthaloyl, trityl, 2-(4-nitrophenylsulfonyl)ethoxycarbonyl, fluorenylmethyloxycarbonyl, benzyloxycarbonyl or *t*-butoxycarbonyl for amino and aminooxy, alkyl for carbonyl and alkyl or trityl for thiol provided that bridge point **Z** is selected from a group consisting of



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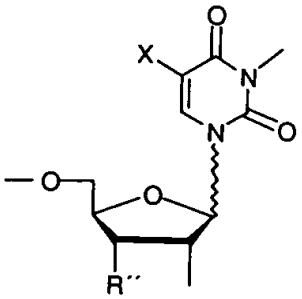

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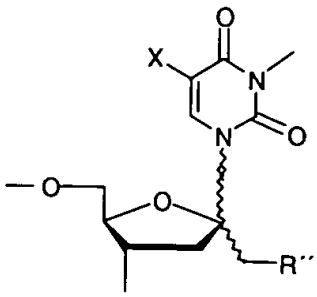

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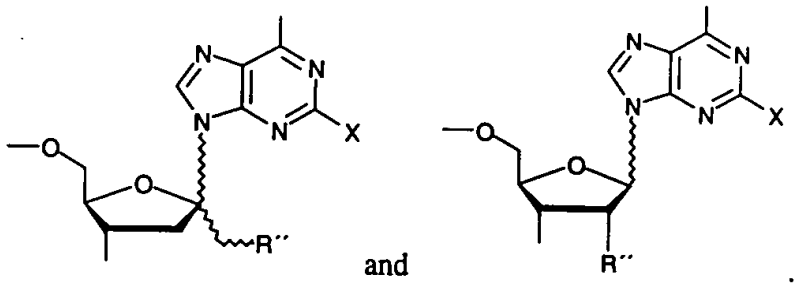


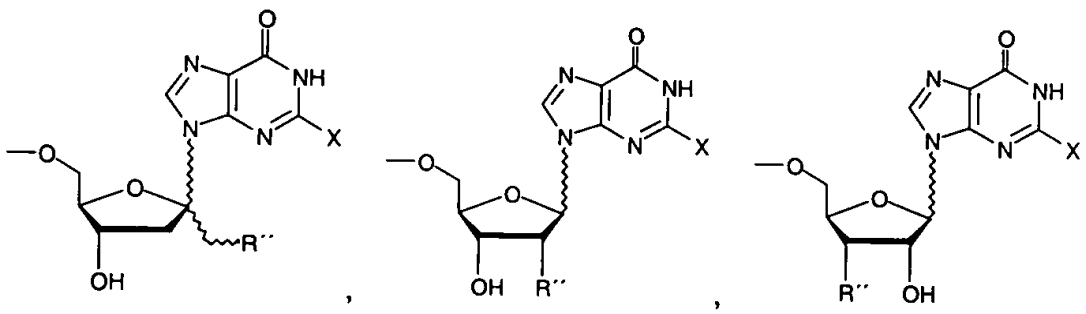
13. (Once Amended) A method for direct attachment of a conjugate group to an oligonucleotide structure enabling the attachment of a desired number of these groups during chain assembly **characterized** in that it comprises a Mitsunobu alkylation of a compound of formula (II)

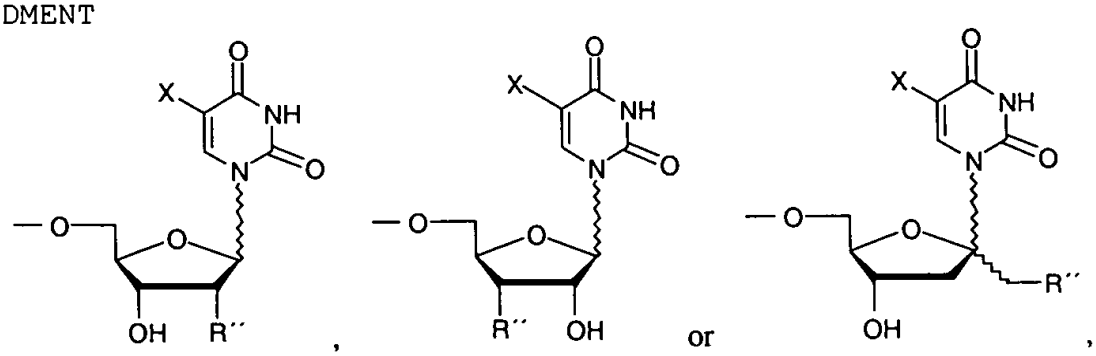
R— Z′ (II)

wherein

R is a temporary protecting group such as DMTr, MMTr, Tr or pixyl;

Z′ is an acidic bridge point selected from a group consisting of





where

R′′ is H or X′X′′, where X′ is -O-, -S-, -N-, ON- or -NH- and X′′ is a permanent protection group such as *t*-butyldimethylsilyl-, tetrahydropyranyl, 1-(2-fluorophenyl)-4-methoxypiperidin-4-yl-, 1-[2-chloro-4-methyl)phenyl]-4-metoxypiperidin-4-yl-, 4-methoxytetrahydropyran-4-yl-, pthaloyl-, acetyl, pivaloyl-, benzoyl-, 4-methylbenzoyl, benzyl-, trityl or alkyl;

X is H, alkyl, alkynyl, allyl, Cl, Br, I, F, S, O, $NHCOCH(CH_3)_2$, $NHCOCH_3$, NHCOPh, SPh_3, $OCOCH_3$ or OCOPh;

and pK_a of said acidic bridge point is <14;

with a compound of formula(III)

G—E′′ (III)

wherein

E′′ is an arm with a primary aliphatic OH group at the end, which arm is formed of one to ten

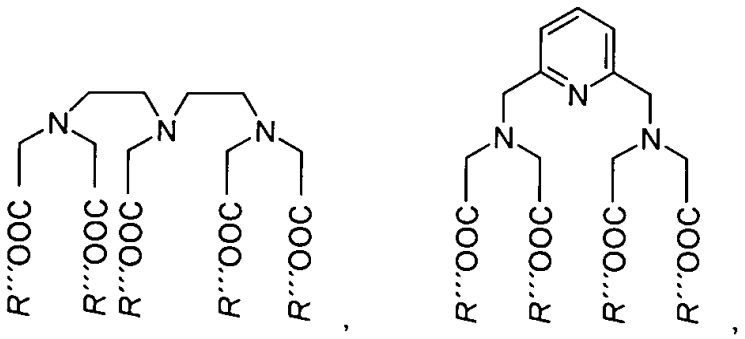
moieties, each moiety being selected from a group consisting of phenylene, alkylene containing 1-12 carbon atoms, ethynediyl (-C≡C-), ether (-O-), thioether (-S-), amide (-CO-NH-, -NH-CO-, -CO-NR′- and -NR′-CO-), carbonyl (-CO-), ester (-COO- and -OOC-), disulfide (-S-S-), diaza (-N=N-), and tertiary amine (-N-R′), wherein R′ represents an alkyl containing less than 5 carbon atoms;

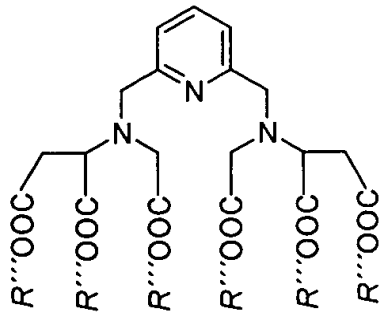
G is a bivalent aromatic structure, tethered to two iminodiacetic acid ester groups [$N(COOR'''')_2$], $N(CH_2COOR'''')_2$ where

R′′′′ is an alkyl of 1 to 4 carbon atoms, allyl, ethyltrimethylsilyl, phenyl or benzyl, which phenyl or benzyl can be substituted or unsubstituted and

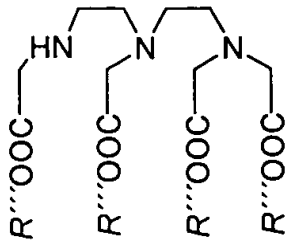
said bivalent aromatic structure is capable of absorbing light or energy and transferring the excitation energy to a lanthanide ion after the solid phase synthesis made labeling reactant has been released from the used solid support, deprotected and converted to a lanthanide chelate, or

G is a structure selected from a group consisting of





and



,

where

R´´´ is an alkyl of 1 to 4 carbon atoms, allyl, ethyltrimethylsilyl, phenyl or benzyl, which phenyl or benzyl can be substituted or unsubstituted, and

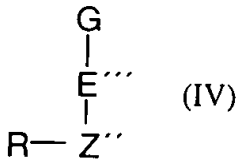
one of the hydrogen atoms is substituted with E´, or

G is a protected functional group, where the functional group is amino, aminooxy, carboxyl, thiol, and the protecting group is pthaloyl, trityl, 2-(4-nitrophenylsulfonyl)ethoxycarbonyl, fluorenylmethyloxycarbonyl, benzyloxycarbonyl or *t*-butoxycarbonyl for amino and aminooxy, alkyl for carbonyl and alkyl or trityl for thiol, or

G is not present; and

the functional groups of E´ and G, excluding said primary aliphatic OH group, are protected;

to produce compound of formula (IV)

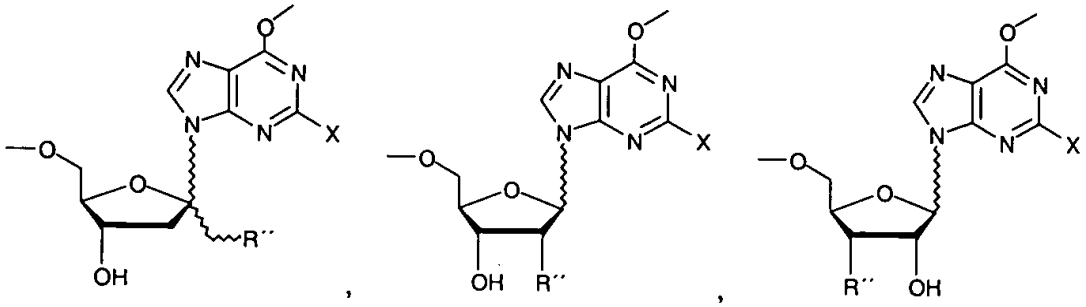


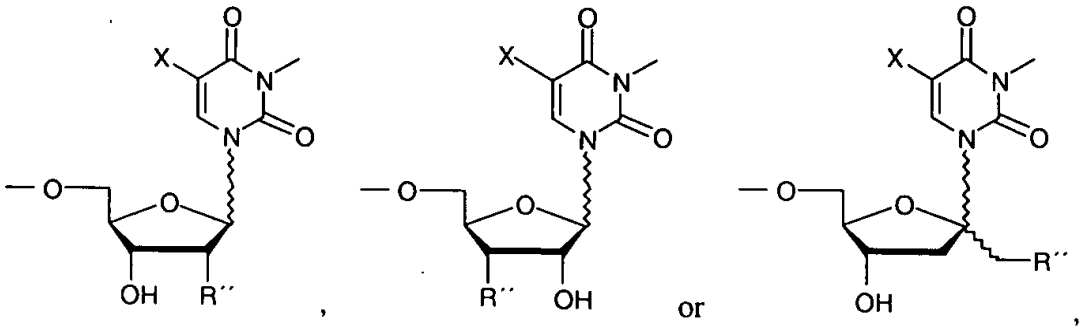
(IV)

wherein G and R of compound (IV) are as defined above;

E''' is a linker arm between **G** and **Z**, and is formed of one to ten moieties, each moiety being selected from a group consisting of phenylene, alkylene containing 1-12 carbon atoms, ethynediyl (-C≡C-), ether (-O-), thioether (-S-), amide (-CO-NH-, -NH-CO-, -CO-NR'- and -NR'-CO-), carbonyl (-CO-), ester (-COO- and -OOC-), disulfide (-S-S-), diaza (-N=N-), and tertiary amine (-N-R'), wherein R' represents an alkyl containing less than 5 carbon atoms; and

Z'' is a bridge point selected from a group consisting of





where

R´´ is H or X´X´´, where X´ is -O-, -S-, -N-, ON- or -NH- and X´´ is a permanent protection group such as *t*-butyldimethylsilyl-, tetrahydropyranyl, 1-(2-fluorophenyl)-4-methoxypiperidin-4-yl-, 1-[2-chloro-4-methyl)phenyl]-4-metoxypiperidin-4-yl-, 4-methoxytetrahydropyran-4-yl-, pthaloyl-, acetyl, pivaloyl-, benzoyl-, 4-methylbenzoyl, benzyl-, trityl or alkyl;

X is H, alkyl, alkynyl, allyl, Cl, Br, I, F, S, O, $NHCOCH(CH_3)_2$, $NHCOCH_3$, NHCOPh, SPh_3, $OCOCH_3$ or OCOPh.